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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,321	10/26/2001	Liming Shao	SPV-045.01	1490

25181 7590 10/21/2004

FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,321	SHAO, LIMING	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 6-21-04 is acknowledged.

Claims included in the prosecution are 26-28.

Claim Rejections - 35 USC ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02256 cited before.

WO discloses cyclodextrin complexes containing fentanyl, alfentanil, sufentanil and lofentanil for the treatment of pain (note the abstract, Examples and claim 16).

WO does not teach all of the claimed compounds falling under the basic structure of fentanyl and although WO teaches only handful compounds including fentanyl, it does not provide specific example using fentanyl. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to encapsulate fentanyl or any compound based on the basic structure of fentanyl in the in the cyclodextrin compositions of WO with a reasonable expectation of success. WO also does not teach the method of treating pain by administering orally or in claimed animals.

However, in the absence of showing otherwise, it is reasonable to expect that the compositions, which are effective in rats, would be effective in other animals and humans too. Determining the mode of administration is deemed to be within the skill of the art and a routine manipulation practiced by an artisan the best possible results.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants once again argues that one of ordinary skill in the art would not have a reasonable expectation of success in a program focused on oral administration of a formulation for the treatment of pain, which formulation comprised cyclodextrins and fentanyl or structurally related compounds. In support, applicant directs the examiner's attention to Shaiova et al (Support Care Cancer, 2004), which according to applicant did not yield analgesia greater than placebo. These arguments are not found to be persuasive. A careful review of the passage quoted by applicant (page 7 of response) indicates that the authors conclude that the dosage amount of fentanyl citrate tested was small and thus, recommend the testing of higher doses. Instant claims do not recite any amounts of Fentanyl or compounds falling under the claimed formula. Applicant further point out to Example 1 in the specification and argue that a 10 % hydroxypropyl-beta-cyclodextrin gave a greater than two-fold improvement in the tail-flick assay 15 minutes after administration of the fentanyl formulation as compared to the saline formulation of fentanyl. These arguments are not found to be persuasive. First of all, it is unclear what the dosages of Fentanyl are. Secondly, the primary reference (WO) encapsulation of fentanyl and derivatives in claimed hydroxypropyl-beta-cyclodextrin and secondary references of Farrer, Portenoy and Stanley clearly

teach the efficacy of fentanyl when administered orally. Therefore, a proper comparison is between the injection modes suggested by WO and the oral administration of the same formulation. Finally, a careful evaluation of the results in Table 1 (instant Example 1) indicates that 10 % gamma HPCD is no better than saline control at 15 minute interval; yet the claims are drawn to generic 'cyclodextrins' with no specific amounts.

4. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/47203 of record.

WO teaches formulations containing narcotic analgesics such as fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration. According to WO, this cyclodextrin is an oral absorption enhancer (abstract, page 7, lines 10-11, examples and claims). Although WO does not teach all the fentanyl based compounds and do not provide examples of fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration, it would have been obvious to one of ordinary skill in the art to use any fentanyl based compound in combination with hydroxypropyl-beta cyclodextrin, with a reasonable expectation of success since it is a absorption enhancer.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the unexpected results. The examiner has already addressed these arguments above.

5. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02256 cited above, further in view of Farrar et al (JNCI, 1998), Portenoy et al (Pain, 1999), Stanley et al (Anesth. Analg. 1989) by themselves (all are of record).

The teachings of WO 92 and WO 99 have been discussed above. What is lacking in these references is the oral administration of the fentanyl-based composition.

The references of Farrar et al, Porenoy et al, Stanley et al and WO each teach the efficacy of fentanyl when administered orally (note abstracts in each). The oral administration of the compositions of fentanyl based compounds, with a reasonable expectation of success would have been obvious to one of ordinary skill in the since the references of Farrar et al, Porenoy et al, Stanley et al show the efficacy of orally administered fentanyl.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the unexpected results. The examiner has already addressed these arguments above.

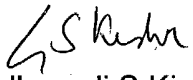
1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK